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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1636	20

DATE MAILED: 08/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/808,388	MASSAAD ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *49* is/are allowed.

6)☒ Claim(s) *26-39,41-48 and 50-52* is/are rejected.

7)☒ Claim(s) *40* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 2/3/03 as Paper No. 16, in which the pending claims were cancelled (claims 1-25) and replaced with new claims 26-52. Claims 26-52 are pending and under consideration in the instant application.

Any rejection of record in the previous office action, mailed 10/03/02 as Paper No. 12, that is not addressed in this action is withdrawn. This action is FINAL.

Oath/Declaration

Receipt is acknowledged of a supplemental declaration, filed 2/3/03 as Paper No. 14. This supplemental declaration has been entered into the file.

Drawings

The corrected or substitute drawings were received on 5/19/03 as Part of Paper No. 19. These drawings are acceptable and have been entered into the file.

Claim Objections

Claim 36 is objected to because of the following informalities: the phrase "The promoter of claim 26, further comprises..." is grammatically incorrect. It would be remedial to change "comprises" to "comprising". Appropriate correction is required.

Claim 39 is objected to because of the following informalities: it recites the term "SEQ ID NOs" which is inappropriate (MPEP 2422.02). It would be remedial to amend the claim to recited "SEQ ID NOS:". Appropriate correction is required.

Claim 41 is objected to because of the following informalities: nucleic acids aren't generally referred to as "encoding" a promoter sequence. It would be remedial to amend the claim to specify a nucleic acid sequence "comprising" the promoter of claim 26. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-38, 41-44, 46-47, 50-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection necessitated by the amendment of the claims in Paper No. 13.**

Each of the claims is drawn towards a hybrid promoter comprising (a) a peroxisome proliferator activated receptor response element (PPAR response element) comprising at least one PPAR-binding site, and (b) a promoter of a type IIA-1 nonpancreatic secreted phospholipase A2 (PLA2s) gene or a functional part of the PLA2s gene. There is not literal support for the phrase "a functional part of a PLA2s gene" in the originally filed specification. This phrase encompasses any portion of the entire PLA2s gene that is functional in some fashion, including coding sequences and 3' sequences that have nothing to do with the promoter region. The

instant specification only has support for a functional portion of the PLA2s promoter, particularly that portion described by SEQ ID NO: 5. Therefore, the cited phrase is impermissible NEW MATTER.

Claim 38 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 38 comprises the limitation of a gene comprising SEQ ID NO: 7, a functional part of SEQ ID NO: 7 or a "variant" of SEQ ID NO: 7, and wherein the gene confers specificity for chondrocytic cells. The specification does not define the term "variant" as applied to SEQ ID NO: 7. A reasonably broad interpretation of the term is that it includes a sequence variation of SEQ ID NO: 7 that retains at least some functionality associated with SEQ ID NO: 7 (e.g. specificity for chondrocytic cells). The specification does not teach from which gene SEQ ID NO: 7 has been derived, only that it confers specificity of expression for chondrocytic cells. The specification doesn't teach what parts of SEQ ID NO: 7 are essential for any function, including conferring specificity of expression for chondrocytic cells. Therefore, the instant specification does not provide any guidance with regard to what changes can be made to SEQ ID NO: 7 such that it will retain functionality.

SEQ ID NO: 7 appears to be novel in the art. Thus, the prior art does not offset the deficiencies of the instant application with regard to providing a basis for the skilled artisan to

envision those changes to SEQ ID NO: 7 which will allow the "part" or "variant" to retains a particular functionality.

Given the lack of any description in the instant specification or prior art as to what parts of SEQ ID NO: 7 can be altered such that the resulting polynucleotide retains any particular activity, including directing chondrocyte-specific expression of an operatively linked gene, one of skill in the art would not have been able to reliably envision even a single embodiments of the broadly claimed genus of "functional parts" or "variants" of SEQ ID NO: 7. Therefore, the skilled artisan would reasonably have concluded applicants were not in possession of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26-38, 40-48, 50-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 is vague and indefinite in that the metes and bounds of the words "hybrid promoter" are unclear. Does the term refer to any promoter having a PPAR element and at least part of the PLA2s promoter? Or does the phrase refer to a recombinant promoter comprising a PPAR element and a heterologous sequence from the PLA2s promoter that is not normally associated with that particular PPAR element? **This rejection is maintained for reasons of record in Paper No. 12 and repeated above.**

Response to Arguments/112 2nd Paragraph

Applicant's arguments filed in Paper No. 16 concerning the term "hybrid promoter" have been fully considered but they are not persuasive. The response essentially argues that the specification clearly defines a "hybrid" promoter and makes clear that such a promoter is constituted by two distinct promoter regions and is produced by collinear union of two fragments of DNA. This argument misses the point the examiner was trying to make. Does the term read on a promoter that comprises heterologous sequences in addition to a sequence comprising (i) PPAR-binding sequences normally associated with the PLA2s promoter and (ii) at least part of the PLA2s promoter? For example, would a hybrid promoter comprising the PPAR and promoter elements taught by Couturier et al (J. Biol. Chemistry, August 1999, Vol. 274, No. 33, pages 23085-23093; see the rejection below) as well as some promoter element obtained from another source be encompassed by the claims? Such a chimeric promoter, comprising a heterologous sequence in addition to the PLA2s PPAR elements and at least part of the PLA2s gene would necessarily have distinct promoter regions and be a collinear union of two fragments of DNA. Or would the term "hybrid" as used in the claims be meant to encompass only those embodiments where the PPAR response element is obtained from a promoter other than the PLA2s promoter? Upon reading the specification it appears this interpretation is the correct one, in which case it would be remedial to amend the claim to clearly indicate that the PPAR response element and PLA2s sequences are heterologous to one another.

The following are all new rejections.

Claims 27-38 all recite the term "the promoter" and are dependent upon claim 26. Claim 26 specifies at least two promoters, the "hybrid" promoter which may further comprise the promoter of a PLA2s gene. Therefore, there is no clear and positive prior antecedent basis for the term "the promoter" in claim 26, upon which claims 27-38 are dependent. It would be remedial to change the term "the promoter" to refer specifically to either the "hybrid" promoter of the "promoter of the PLA2s gene". **This is a new rejection necessitated by the amendment of the claims in Paper No. 16.**

Claim 36 is vague and indefinite in that the metes and bounds of the phrase "The promoter...further comprises a gene that confers tissue specificity..." are unclear. It is unclear how a promoter can comprise a gene. **This is a new rejection necessitated by the amendment of the claims in Paper No. 16.**

Claim 37 is vague and indefinite in that there is no clear and positive prior antecedent basis for the term "the chondrocytic cells". It would be remedial to amend the claim by deleting "the" from the term. **This is a new rejection necessitated by the amendment of the claims in Paper No. 16.**

Claim 40 is vague and indefinite in that there is no clear and positive prior antecedent basis for the term "the nucleic acid" in claim 39, upon which claim 40 is dependent. It would be remedial to amend claim 39 in order to provide an antecedent basis for the term (e.g. A nucleic acid comprising the nucleic acid sequence of...."). **This is a new rejection necessitated by the amendment of the claims in Paper No. 16.**

Claim 42 is vague and indefinite in that there is no clear and positive prior antecedent basis for the term "said nucleic acid" in claims 26 and 35, upon which claim 42 is dependent.

Claim 45 is vague and indefinite in that there is no clear and positive prior antecedent basis for the term "a nucleic acid according to claim 39". **This is a new rejection necessitated by the amendment of the claims in Paper No. 16.**

Claim 48 is vague and indefinite in that the metes and bounds of the term "class" are not clear. It is not clear whether the term "class" means some classification for the recited nucleic acid sequence (e.g. PPAR-binding sites), or if the term is meant to refer to a group consisting of the recited sequences. It appears that the claim is intended to recite a Markush group comprising the recited sequences, in which case it would be remedial to amend the claim to read the "group consisting of..." rather than the "class". **This is a new rejection necessitated by the amendment of the claims in Paper No. 16.**

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 39 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claim 39 recites a "... nucleic acid sequence...comprising...a functional variant of SEQ ID NOS: 1, 2, 3, 4 or 5". The term nucleic acid sequence is interpreted to mean a nucleic acid of a given sequence. The open claim language and the extremely broad scope encompassed by the term "functional variant" as applied to the instant invention means that the claim reads on any gene found in nature that comprises a PPAR-binding sequence that maintains any function of the nucleic acids encoded by SEQ ID NOS: 1-4. The claim also reads on the PLA2s gene as found

in nature, since applicants teach that SEQ ID NO: 5 corresponds to nucleotides -247 to +20 of the human PLA2s IIA gene (page 11, lines 15-16). It would be remedial to amend the claims to indicate the "hand of man" (e.g. "an isolated nucleic acid comprising").

Claims 50-52 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. **This is a new rejection necessitated by the amendment of the claims in Paper No. 16.**

Each of the claims is directed to a cell comprising a hybrid promoter or vector of the invention. The instant specification teaches that one can use the nucleic acids of the invention *in vivo* (e.g. treatment of a human subject via gene therapy). Because the claims encompass a cell in a human subject, the claims can be read as reading on a human. Therefore, the cells are directed to non statutory subject matter. It would be remedial to amend the claim to recite an "isolated" cell.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The term "functional variant" as defined in the specification is extremely broad in scope and encompasses any change in sequence so long as the altered sequence retains functionality. For example, for PPAR binding sites it can reasonably be read to indicate that the "variant" retains the ability to bind a PPAR (e.g. page 7, lines 15-17).

Claim 39 is rejected under 35 U.S.C. 102(a) as being anticipated by Couturier et al (J. Biol. Chemistry, August 1999, Vol. 274, No. 33, pages 23085-23093; see the entire document). **This is a new rejection necessitated by applicants' amendment of the claims in Paper No. 16.**

Couturier et al describe the characterization of the PLA2s gene and those elements that are responsible for regulating transcription of the gene. Couturier et al demonstrate that the rat PLA2s promoter comprises at least one PPAR-binding element with extensive homology with a known PPRA-binding element (e.g. DR1) (e.g. page 23090, column 2, 4th paragraph; Figure 9). The PPAR binding elements described by Couturier et al would necessarily qualify as "functional variants" of the PPAR-binding elements described by SEQ ID NOS: 1-4. The rat PLA2s promoter region described by PLA2s can reasonably be considered as a "functional variant" of SEQ ID NO: 5.

Claim 39 is rejected under 35 U.S.C. 102(e) as being anticipated by Evans et al (U.S. Patent No. 6,413,994). **This is a new rejection necessitated by applicants' amendment of the claims in Paper No. 16.**

Evans et al teach the use of PPARγ-binding elements operatively linked to a reporter gene under control of the thymidine kinase promoter in order to identify compounds that modulate the activity of PPARγ (e.g. the Abstract, Example 2). The hybrid promoter taught by Evans et al comprises "functional variants" of the PPAR-binding elements described by SEQ ID NOS: 1-4.

Conclusion

Claim 49 is allowed. Claim 40 is objected to as being dependent upon a rejected claim. Claims 26-39, 41-48, 50-52 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr., PhD
Examiner
Art Unit 1636

Ggl
August 7, 2003